Clinical trial results:
A multi-center, open label, single-arm study to investigate the safety and efficacy of daily oral administration of 2 mg dienogest tablets for the treatment of endometriosis in adolescents over a treatment period of 52 weeks

Summary

EudraCT number	2009-017169-53
Trial protocol	ES FI DE AT FR CZ
Global end of trial date	12 September 2013

Results information

Result version number	v2 (current)
This version publication date	04 September 2016
First version publication date	28 June 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY86-5258/13788

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01283724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000147-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the influence of long-term oral administration of dienogest 2 milligram (mg) once a day, on bone mineral density (BMD) of the spine, measured by dual-energy X-ray absorptiometry (DEXA) in adolescents with confirmed or clinically suspected endometriosis.

Protection of trial subjects:

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, were designed to ensure that the sponsor and investigator abide by Good Clinical Practice guidelines, the Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric population (International Conference of Harmonization [ICH] topic E11 – Committee for Medicinal Products for Human Use (CHMP)/ICH/2711/99), and under the guiding principles detailed in the Declaration of Helsinki. As applicable according to local regulations, the protocol and all protocol amendments were reviewed and approved by each pertinent Competent Authority. Each subject and legal representative(s) or proxy consenter(s) had ample time and opportunity to ask questions and was informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision. If at any time the subject had doubts or concerns regarding study procedures or investigations, the investigator had to stop the examination and had to take enough time to assess the reason and discuss the willingness of further participation with the subject. The subject entered the study only if the subject and legal representative(s) or proxy consenter(s) voluntarily agreed to sign the informed consent/ assent form and had done so. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug. The design of the study was discussed with and agreed by the Pediatric Committee of the European Medicines Agency.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Czech Republic: 50
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	France: 5

Country: Number of subjects enrolled	Germany: 16
Worldwide total number of subjects	111
EEA total number of subjects	111

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	111
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 21 study centers in 6 countries: Austria, Czech Republic, Finland, France, Germany, and Spain. Girls from menarche until less than 18 years of age were considered to be appropriate with confirmed or clinically suspected endometriosis were recruited.

Pre-assignment

Screening details:

Out of 120 subjects screened, 111 were assigned to treatment and 9 were listing-only subjects (LOS) who did not receive the treatment. Of these 9 LOS, 8 were screening failures and 1 subject withdrew from the study before start of treatment.

Period 1

Period 1 title	Overall study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dienogest (Visanne, BAY86-5258)

Arm description:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Dienogest
Investigational medicinal product code	BAY86-5258
Other name	Visanne
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

Number of subjects in period 1	Dienogest (Visanne, BAY86-5258)
Started	111
Received treatment	111
Entered Follow up period 1	111
Completed treatment	97
Completed	97
Not completed	14
Consent withdrawn by subject	6
Adverse event, non-fatal	5
Noncompliance with study drug	1
Lost to follow-up	1
Lack of efficacy	1

Period 2

Period 2 title	Follow-up period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dienogest (Visanne, BAY86-5258)

Arm description:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Dienogest
Investigational medicinal product code	BAY86-5258
Other name	Visanne
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

Number of subjects in period 2[1]	Dienogest (Visanne, BAY86-5258)
Started	61
Completed	61

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A total of 111 subjects started Follow-up period 1 (a follow-up assessment of 4 weeks after the end of treatment) out of which 107 subjects completed and reasons for non-completion of 4 subjects were consent withdrawn in 2 subjects and lost to follow-up in 2 subjects. A total of 61 subjects with a decrease in BMD at the end of treatment, started and completed Follow-up period 2 (a follow-up assessment for 26 weeks after the end of treatment).

Baseline characteristics

Reporting groups	
Reporting group title	Dienogest (Visanne, BAY86-5258)
Reporting group description:	
Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.	

Reporting group values	Dienogest (Visanne, BAY86-5258)	Total	
Number of subjects	111	111	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	15.4		
standard deviation	± 1.3	-	
Gender categorical Units: Subjects			
Female	111	111	
Race Units: Subjects			
White	105	105	
Black or African American	1	1	
Not recorded	5	5	
Ethnicity Units: Subjects			
Not Hispanic or Latino	105	105	
Hispanic or Latino	1	1	
Not recorded	5	5	

End points

End points reporting groups

Reporting group title	Dienogest (Visanne, BAY86-5258)
Reporting group description:	
Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.	
Reporting group title	Dienogest (Visanne, BAY86-5258)
Reporting group description:	
Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS consisted of 111 subjects and was defined as the set of all subjects who took at least one unit of study drug and if at least one observation after drug administration was available.	

Primary: Relative Percent Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA)

End point title	Relative Percent Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA)[1]
End point description:	
The measurement of BMD by DEXA is the gold standard method for investigation of bone mass.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed since descriptive statistical analysis was only planned for this endpoint.

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	103[2]			
Units: percent change				
arithmetic mean (standard deviation)	-1.2 (± 2.3)			

Notes:

[2] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Percent Change From Baseline in Whole Body Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA)

End point title	Relative Percent Change From Baseline in Whole Body Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA)
End point description:	
The measurement of BMD by DEXA is the gold standard method for investigation of bone mass.	

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	102[3]			
Units: percent change				
arithmetic mean (standard deviation)	0.8 (± 1.6)			

Notes:

[3] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Z-scores at Week 52

End point title	Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Z-scores at Week 52

End point description:

Based on the BMD values and the weight, the age-normalized percentiles (Z-scores) were determined to allow for comparison with historical control groups. “No difference” in comparison with the historical control groups was defined as a Z-score between '-0.5' and '0.5', a lower value was defined as a value below '-0.5', and a higher value above '0.5'.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	103[4]			
Units: Z-score				
arithmetic mean (standard deviation)	-0.3188 (± 0.2649)			

Notes:

[4] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Whole Body Z-scores at Week 52

End point title	Change From Baseline in Whole Body Z-scores at Week 52

End point description:

Based on the BMD values and the weight, the age-normalized percentiles (Z-scores) were determined to allow for comparison with historical control groups. "No difference" in comparison with the historical control groups was defined as a Z-score between '-0.5' and '0.5', a lower value was defined as a value below '-0.5', and a higher value above '0.5'.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	102[5]			
Units: Z-score				
arithmetic mean (standard deviation)	-0.0609 (± 0.3181)			

Notes:

[5] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders at Week 24

End point title	Percentage of Responders at Week 24

End point description:

Responders were defined as subjects with reduction in pain intensity from baseline of at least 30% in the Visual Analog Scale (VAS) at Week 24. VAS consisted of a 100 unit long straight line, with verbal anchors at either end, representing a continuum of pain intensity. One end of the line with 0 score as "absence of pain" while the other end of the line with 100 score as "unbearable pain". The assessment of pelvic pain on a VAS was done once every 4 weeks till the end of the treatment (Week 52).

End point type	Secondary

End point timeframe:

Week 24

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	100[6]			
Units: Percentage of subjects				
number (not applicable)				
Yes	81			
No	19			

Notes:

[6] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Change From Baseline in Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

The cardinal symptoms inlcuded in the modified Biberoglu and Behrman severity profile were pelvic pain, dysmenorrhea, and dyspareunia (the latter only in those subjects having sexual intercourse), analyzed at all visits with symptom severity scores from 0 (none) to 3 (severe). Negative value for change from baseline indicates an improvement. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	110[7]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (N=107)	-0.757 (± 0.9985)			
Change at Week 8 (N=106)	-1.0094 (± 0.971)			
Change at Week 12 (N=103)	-1.0291 (± 1.0333)			
Change at Week 16 (N=100)	-1.05 (± 1.0481)			
Change at Week 20 (N=97)	-1.0825 (± 0.9754)			
Change at Week 24 (N=99)	-1.2424 (± 0.9699)			
Change at Week 28 (N=97)	-1.2062 (± 0.9889)			
Change at Week 32 (N=97)	-1.2165 (± 1.0127)			
Change at Week 36 (N=95)	-1.2421 (± 1.0181)			
Change at Week 40 (N=97)	-1.3402 (± 0.967)			
Change at Week 44 (N=94)	-1.383 (± 0.9849)			
Change at Week 48 (N=94)	-1.4255 (± 0.8858)			
Change at Week 52 (N=103)	-1.3786 (± 0.9713)			

Notes:

[7] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Change From Baseline in Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

The cardinal symptoms inlcuded in the modified Biberoglu and Behrman severity profile were pelvic pain, dysmenorrhea, and dyspareunia (the latter only in those subjects having sexual intercourse), analyzed at all visits with symptom severity scores from 0 (none) to 3 (severe). Negative value for change from baseline indicates an improvement. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	110[8]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (N=107)	-0.7944 (± 1.1221)			
Change at Week 8 (N=106)	-1.3208 (± 1.1343)			
Change at Week 12 (N=103)	-1.4854 (± 1.1014)			
Change at Week 16 (N=100)	-1.43 (± 1.0565)			
Change at Week 20 (N=97)	-1.5876 (± 1.0483)			
Change at Week 24 (N=99)	-1.5657 (± 1.0016)			
Change at Week 28 (N=97)	-1.5361 (± 1.0314)			
Change at Week 32 (N=97)	-1.5773 (± 1.1165)			
Change at Week 36 (N=95)	-1.5579 (± 1.1914)			
Change at Week 40 (N=97)	-1.7113 (± 1.0304)			
Change at Week 44 (N=94)	-1.7447 (± 1.0363)			
Change at Week 48 (N=94)	-1.7447 (± 1.0466)			
Change at Week 52 (N=103)	-1.7379 (± 0.9596)			

Notes:

[8] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Change From Baseline in Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

The cardinal symptoms inlcuded in the modified Biberoglu and Behrman severity profile were pelvic pain, dysmenorrhea, and dyspareunia (the latter only in those subjects having sexual intercourse), analyzed at all visits with symptom severity scores from 0 (none) to 3 (severe). Subjects evaluated the cardinal symptoms using modified Biberoglu and Behrman severity profile in an e-diary over the whole treatment period. Negative value for change from baseline indicates an improvement. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	21[9]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (N=13)	-0.1538 (± 0.6887)			
Change at Week 8 (N=15)	-0.2667 (± 0.7988)			
Change at Week 12 (N=15)	-0.2667 (± 0.8837)			
Change at Week 16 (N=17)	-0.1765 (± 1.0744)			
Change at Week 20 (N=15)	-0.4 (± 0.8281)			
Change at Week 24 (N=12)	-0.25 (± 0.6216)			
Change at Week 28 (N=13)	-0.4615 (± 0.7763)			
Change at Week 32 (N=14)	-0.3571 (± 0.8419)			
Change at Week 36 (N=13)	-0.2308 (± 0.725)			
Change at Week 40 (N=14)	-0.3571 (± 0.7449)			
Change at Week 44 (N=12)	-0.5833 (± 1.0836)			
Change at Week 48 (N=13)	-0.4615 (± 1.45)			
Change at Week 52 (N=13)	-0.2308 (± 0.725)			

Notes:

[9] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Percentage of Subjects With Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of pelvic pain was assessed using a rating scale: missing; 0 = none; 1 = mild (occasional pelvic discomfort); 2 = moderate (noticeable discomfort for most of the cycle); 3 = severe (requires strong analgesics and persists during cycle when not menstruating) based on the subject's self-assessment of symptoms. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	110[10]			
Units: Percentage of subjects				
number (not applicable)				
Baseline (N=110): missing	0			
Baseline (N=110): none	9.1			
Baseline (N=110): mild	23.6			
Baseline (N=110): moderate	52.7			
Baseline (N=110): severe	14.5			
Week 4 (N=108): missing	0			
Week 4 (N=108): none	35.2			
Week 4 (N=108): mild	40.7			
Week 4 (N=108): moderate	16.7			
Week 4 (N=108): severe	7.4			
Week 8 (N=107): missing	0			
Week 8 (N=107): none	44.9			
Week 8 (N=107): mild	42.1			
Week 8 (N=107): moderate	8.4			
Week 8 (N=107): severe	4.7			
Week 12 (N=104): missing	0			
Week 12 (N=104): none	53.8			
Week 12 (N=104): mild	26			
Week 12 (N=104): moderate	16.3			
Week 12 (N=104): severe	3.8			
Week 16 (N=101): missing	0			
Week 16 (N=101): none	47.5			
Week 16 (N=101): mild	38.6			
Week 16 (N=101): moderate	12.9			
Week 16 (N=101): severe	1			
Week 20 (N=98): missing	0			

Week 20 (N=98): none	48			
Week 20 (N=98): mild	38.8			
Week 20 (N=98): moderate	13.3			
Week 20 (N=98): severe	0			
Week 24 (N=100): missing	0			
Week 24 (N=100): none	60			
Week 24 (N=100): mild	30			
Week 24 (N=100): moderate	7			
Week 24 (N=100): severe	3			
Week 28 (N=98): missing	0			
Week 28 (N=98): none	57.1			
Week 28 (N=98): mild	32.7			
Week 28 (N=98): moderate	8.2			
Week 28 (N=98): severe	2			
Week 32 (N=98): missing	0			
Week 32 (N=98): none	59.2			
Week 32 (N=98): mild	31.6			
Week 32 (N=98): moderate	6.1			
Week 32 (N=98): severe	3.1			
Week 36 (N=96): missing	0			
Week 36 (N=96): none	61.5			
Week 36 (N=96): mild	29.2			
Week 36 (N=96): moderate	7.3			
Week 36 (N=96): severe	2.1			
Week 40 (N=98): missing	0			
Week 40 (N=98): none	66.3			
Week 40 (N=98): mild	29.6			
Week 40 (N=98): moderate	3.1			
Week 40 (N=98): severe	1			
Week 44 (N=95): missing	0			
Week 44 (N=95): none	69.5			
Week 44 (N=95): mild	25.3			
Week 44 (N=95): moderate	4.2			
Week 44 (N=95): severe	1.1			
Week 48 (N=95): missing	0			
Week 48 (N=95): none	73.7			
Week 48 (N=95): mild	23.2			
Week 48 (N=95): moderate	3.2			
Week 48 (N=95): severe	0			
Week 52 (N=104): missing	0			
Week 52 (N=104): none	71.2			
Week 52 (N=104): mild	24			
Week 52 (N=104): moderate	3.8			
Week 52 (N=104): severe	1			

Notes:

[10] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Percentage of Subjects With Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of dysmenorrhea was assessed using a rating scale: missing; 0 = none; 1 = mild (some loss in work efficiency); 2 = moderate (in bed part of day, occasional loss of work efficiency); 3 = severe (in bed one or more days, incapacitation) based on the subject's self-assessment of symptoms. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	110[11]			
Units: Percentage of subjects				
number (not applicable)				
Baseline (N=110): missing	0			
Baseline (N=110): none	3.6			
Baseline (N=110): mild	21.8			
Baseline (N=110): moderate	47.3			
Baseline (N=110): severe	27.3			
Week 4 (N=108): missing	0			
Week 4 (N=108): none	30.6			
Week 4 (N=108): mild	29.6			
Week 4 (N=108): moderate	28.7			
Week 4 (N=108): severe	11.1			
Week 8 (N=107): missing	0			
Week 8 (N=107): none	57			
Week 8 (N=107): mild	20.6			
Week 8 (N=107): moderate	21.5			
Week 8 (N=107): severe	0.9			
Week 12 (N=104): missing	0			
Week 12 (N=104): none	62.5			
Week 12 (N=104): mild	27.9			
Week 12 (N=104): moderate	8.7			
Week 12 (N=104): severe	1			
Week 16 (N=101): missing	0			
Week 16 (N=101): none	61.4			
Week 16 (N=101): mild	25.7			
Week 16 (N=101): moderate	12.9			
Week 16 (N=101): severe	0			
Week 20 (N=98): missing	0			
Week 20 (N=98): none	73.5			
Week 20 (N=98): mild	18.4			
Week 20 (N=98): moderate	6.1			
Week 20 (N=98): severe	2			

Week 24 (N=100): missing	0			
Week 24 (N=100): none	70			
Week 24 (N=100): mild	20			
Week 24 (N=100): moderate	8			
Week 24 (N=100): severe	2			
Week 28 (N=98): missing	0			
Week 28 (N=98): none	69.4			
Week 28 (N=98): mild	19.4			
Week 28 (N=98): moderate	8.2			
Week 28 (N=98): severe	3.1			
Week 32 (N=98): missing	0			
Week 32 (N=98): none	73.5			
Week 32 (N=98): mild	17.3			
Week 32 (N=98): moderate	6.1			
Week 32 (N=98): severe	3.1			
Week 36 (N=96): missing	0			
Week 36 (N=96): none	71.9			
Week 36 (N=96): mild	16.7			
Week 36 (N=96): moderate	8.3			
Week 36 (N=96): severe	3.1			
Week 40 (N=98): missing	0			
Week 40 (N=98): none	80.6			
Week 40 (N=98): mild	12.2			
Week 40 (N=98): moderate	6.1			
Week 40 (N=98): severe	1			
Week 44 (N=95): missing	0			
Week 44 (N=95): none	76.8			
Week 44 (N=95): mild	20			
Week 44 (N=95): moderate	3.2			
Week 44 (N=95): severe	0			
Week 48 (N=95): missing	0			
Week 48 (N=95): none	83.2			
Week 48 (N=95): mild	11.6			
Week 48 (N=95): moderate	4.2			
Week 48 (N=95): severe	1.1			
Week 52 (N=104): missing	0			
Week 52 (N=104): none	78.8			
Week 52 (N=104): mild	15.4			
Week 52 (N=104): moderate	5.8			
Week 52 (N=104): severe	0			

Notes:

[11] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Percentage of Subjects With Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of dyspareunia was assessed using a rating scale: missing; 0 = none (no pain during intercourse); 1 = mild (tolerated discomfort); 2 = moderate (intercourse painful to the point of causing interdiction); 3 = severe (avoids intercourse because of pain) based on the subject's self-assessment of symptoms. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	110[12]			
Units: Percentage of subjects				
number (not applicable)				
Baseline (N=110): missing	80.9			
Baseline (N=110): none	9.1			
Baseline (N=110): mild	5.5			
Baseline (N=110): moderate	3.6			
Baseline (N=110): severe	0.9			
Week 4 (N=108): missing	80.6			
Week 4 (N=108): none	12			
Week 4 (N=108): mild	3.7			
Week 4 (N=108): moderate	3.7			
Week 4 (N=108): severe	0			
Week 8 (N=107): missing	75.7			
Week 8 (N=107): none	15			
Week 8 (N=107): mild	6.5			
Week 8 (N=107): moderate	2.8			
Week 8 (N=107): severe	0			
Week 12 (N=104): missing	74			
Week 12 (N=104): none	16.3			
Week 12 (N=104): mild	7.7			
Week 12 (N=104): moderate	1.9			
Week 12 (N=104): severe	0			
Week 16 (N=101): missing	71.3			
Week 16 (N=101): none	16.8			
Week 16 (N=101): mild	6.9			
Week 16 (N=101): moderate	4			
Week 16 (N=101): severe	1			
Week 20 (N=98): missing	70.4			
Week 20 (N=98): none	19.4			
Week 20 (N=98): mild	7.1			
Week 20 (N=98): moderate	3.1			
Week 20 (N=98): severe	0			
Week 24 (N=100): missing	75			
Week 24 (N=100): none	18			
Week 24 (N=100): mild	4			
Week 24 (N=100): moderate	3			

Week 24 (N=100): severe	0			
Week 28 (N=98): missing	73.5			
Week 28 (N=98): none	18.4			
Week 28 (N=98): mild	5.1			
Week 28 (N=98): moderate	3.1			
Week 28 (N=98): severe	0			
Week 32 (N=98): missing	65.3			
Week 32 (N=98): none	25.5			
Week 32 (N=98): mild	6.1			
Week 32 (N=98): moderate	3.1			
Week 32 (N=98): severe	0			
Week 36 (N=96): missing	63.5			
Week 36 (N=96): none	24			
Week 36 (N=96): mild	7.3			
Week 36 (N=96): moderate	5.2			
Week 36 (N=96): severe	0			
Week 40 (N=98): missing	68.4			
Week 40 (N=98): none	20.4			
Week 40 (N=98): mild	7.1			
Week 40 (N=98): moderate	2			
Week 40 (N=98): severe	2			
Week 44 (N=95): missing	63.2			
Week 44 (N=95): none	23.2			
Week 44 (N=95): mild	10.5			
Week 44 (N=95): moderate	2.1			
Week 44 (N=95): severe	1.1			
Week 48 (N=95): missing	64.2			
Week 48 (N=95): none	28.4			
Week 48 (N=95): mild	4.2			
Week 48 (N=95): moderate	1.1			
Week 48 (N=95): severe	2.1			
Week 52 (N=104): missing	66.3			
Week 52 (N=104): none	23.1			
Week 52 (N=104): mild	4.8			
Week 52 (N=104): moderate	3.8			
Week 52 (N=104): severe	1.9			

Notes:

[12] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Pelvic Tenderness Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Percentage of Subjects With Pelvic Tenderness Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of pelvic tenderness was assessed using a rating scale: missing; 0 = none (no pain during intercourse); 1 = mild (minimal tenderness on palpation); 2 = moderate (extensive tenderness on palpation); 3 = severe (unable to palpate because of tenderness) based on the gynecological palpation by the attending physician. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	111[13]			
Units: Percentage of subjects				
number (not applicable)				
Baseline (N=33): missing	0			
Baseline (N=33): none	63.6			
Baseline (N=33): mild	30.3			
Baseline (N=33): moderate	6.1			
Baseline (N=33): severe	0			
Week 4 (N=39): missing	0			
Week 4 (N=39): none	66.7			
Week 4 (N=39): mild	28.2			
Week 4 (N=39): moderate	5.1			
Week 4 (N=39): severe	0			
Week 8 (N=45): missing	0			
Week 8 (N=45): none	64.4			
Week 8 (N=45): mild	28.9			
Week 8 (N=45): moderate	6.7			
Week 8 (N=45): severe	0			
Week 12 (N=48): missing	0			
Week 12 (N=48): none	77.1			
Week 12 (N=48): mild	18.8			
Week 12 (N=48): moderate	4.2			
Week 12 (N=48): severe	0			
Week 16 (N=43): missing	0			
Week 16 (N=43): none	79.1			
Week 16 (N=43): mild	18.6			
Week 16 (N=43): moderate	2.3			
Week 16 (N=43): severe	0			
Week 20 (N=38): missing	0			
Week 20 (N=38): none	89.5			
Week 20 (N=38): mild	7.9			
Week 20 (N=38): moderate	2.6			
Week 20 (N=38): severe	0			
Week 24 (N=53): missing	0			
Week 24 (N=53): none	83			
Week 24 (N=53): mild	15.1			
Week 24 (N=53): moderate	1.9			
Week 24 (N=53): severe	0			
Week 28 (N=40): missing	0			
Week 28 (N=40): none	87.5			
Week 28 (N=40): mild	12.5			

Week 28 (N=40): moderate	0			
Week 28 (N=40): severe	0			
Week 32 (N=37): missing	0			
Week 32 (N=37): none	91.9			
Week 32 (N=37): mild	8.1			
Week 32 (N=37): moderate	0			
Week 32 (N=37): severe	0			
Week 36 (N=46): missing	0			
Week 36 (N=46): none	89.1			
Week 36 (N=46): mild	6.5			
Week 36 (N=46): moderate	4.3			
Week 36 (N=46): severe	0			
Week 40 (N=38): missing	0			
Week 40 (N=38): none	86.8			
Week 40 (N=38): mild	13.2			
Week 40 (N=38): moderate	0			
Week 40 (N=38): severe	0			
Week 44 (N=39): missing	0			
Week 44 (N=39): none	87.2			
Week 44 (N=39): mild	10.3			
Week 44 (N=39): moderate	2.6			
Week 44 (N=39): severe	0			
Week 48 (N=38): missing	0			
Week 48 (N=38): none	94.7			
Week 48 (N=38): mild	5.3			
Week 48 (N=38): moderate	0			
Week 48 (N=38): severe	0			
Week 52 (N=56): missing	0			
Week 52 (N=56): none	80.4			
Week 52 (N=56): mild	17.9			
Week 52 (N=56): moderate	1.8			
Week 52 (N=56): severe	0			

Notes:

[13] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Induration Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point title	Percentage of Subjects With Induration Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of induration was assessed using a rating scale: missing; 0 = none (no pain during intercourse); 1 = mild (uterus freely mobile, induration in the cul-de-sac); 2 = moderate (thickened and indurated adnexa and cul-de-sac, restricted uterine mobility); 3 = severe (nodular adnexa and cul-de-sac, uterus frequently frozen) based on the gynecological palpation by the attending physician. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	111[14]			
Units: Percentage of subjects				
number (not applicable)				
Baseline (N=33): missing	24.2			
Baseline (N=33): none	60.6			
Baseline (N=33): mild	15.2			
Baseline (N=33): moderate	0			
Baseline (N=33): severe	0			
Week 4 (N=39): missing	20.5			
Week 4 (N=39): none	71.8			
Week 4 (N=39): mild	7.7			
Week 4 (N=39): moderate	0			
Week 4 (N=39): severe	0			
Week 8 (N=45): missing	22.2			
Week 8 (N=45): none	68.9			
Week 8 (N=45): mild	8.9			
Week 8 (N=45): moderate	0			
Week 8 (N=45): severe	0			
Week 12 (N=48): missing	18.8			
Week 12 (N=48): none	81.3			
Week 12 (N=48): mild	0			
Week 12 (N=48): moderate	0			
Week 12 (N=48): severe	0			
Week 16 (N=43): missing	18.6			
Week 16 (N=43): none	79.1			
Week 16 (N=43): mild	2.3			
Week 16 (N=43): moderate	0			
Week 16 (N=43): severe	0			
Week 20 (N=38): missing	21.1			
Week 20 (N=38): none	78.9			
Week 20 (N=38): mild	0			
Week 20 (N=38): moderate	0			
Week 20 (N=38): severe	0			
Week 24 (N=53): missing	18.9			
Week 24 (N=53): none	75.5			
Week 24 (N=53): mild	5.7			
Week 24 (N=53): moderate	0			
Week 24 (N=53): severe	0			
Week 28 (N=40): missing	20			
Week 28 (N=40): none	80			
Week 28 (N=40): mild	0			
Week 28 (N=40): moderate	0			
Week 28 (N=40): severe	0			
Week 32 (N=37): missing	18.9			

Week 32 (N=37): none	81.1			
Week 32 (N=37): mild	0			
Week 32 (N=37): moderate	0			
Week 32 (N=37): severe	0			
Week 36 (N=46): missing	19.6			
Week 36 (N=46): none	78.3			
Week 36 (N=46): mild	2.2			
Week 36 (N=46): moderate	0			
Week 36 (N=46): severe	0			
Week 40 (N=38): missing	21.1			
Week 40 (N=38): none	78.9			
Week 40 (N=38): mild	0			
Week 40 (N=38): moderate	0			
Week 40 (N=38): severe	0			
Week 44 (N=39): missing	20.5			
Week 44 (N=39): none	79.5			
Week 44 (N=39): mild	0			
Week 44 (N=39): moderate	0			
Week 44 (N=39): severe	0			
Week 48 (N=38): missing	18.4			
Week 48 (N=38): none	78.9			
Week 48 (N=38): mild	2.6			
Week 48 (N=38): moderate	0			
Week 48 (N=38): severe	0			
Week 52 (N=56): missing	10.7			
Week 52 (N=56): none	87.5			
Week 52 (N=56): mild	1.8			
Week 52 (N=56): moderate	0			
Week 52 (N=56): severe	0			

Notes:

[14] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Investigator

End point title	Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Investigator

End point description:

The investigator rating scale used in this study was based on the validated CGI scale, which is widely used as a simple tool to assess the overall effect of treatments. The investigator or a sub-investigator rated the total improvement according to the following scale: Score 1 = very much improved; Score 2 = much improved; Score 3 = minimally improved; Score 4 = no change; Score 5 = minimally worse; Score 6 = much worse; Score 7 = very much worse.
None of the subjects reported Score 7. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 36, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	111[15]			
Units: Percentage of subjects				
number (not applicable)				
Week 12 (N=104): Score=1	39.4			
Week 12 (N=104): Score=2	46.2			
Week 12 (N=104): Score=3	10.6			
Week 12 (N=104): Score=4	2.9			
Week 12 (N=104): Score=5	1			
Week 12 (N=104): Score=6	0			
Week 24 (N=102): Score=1	64.7			
Week 24 (N=102): Score=2	27.5			
Week 24 (N=102): Score=3	5.9			
Week 24 (N=102): Score=4	2			
Week 24 (N=102): Score=5	0			
Week 24 (N=102): Score=6	0			
Week 36 (N=98): Score=1	67.3			
Week 36 (N=98): Score=2	24.5			
Week 36 (N=98): Score=3	6.1			
Week 36 (N=98): Score=4	0			
Week 36 (N=98): Score=5	1			
Week 36 (N=98): Score=6	1			
Week 52 (N=109): Score=1	64.2			
Week 52 (N=109): Score=2	25.7			
Week 52 (N=109): Score=3	4.6			
Week 52 (N=109): Score=4	3.7			
Week 52 (N=109): Score=5	1.8			
Week 52 (N=109): Score=6	0			

Notes:

[15] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Subject

End point title	Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Subject

End point description:

The subject rating scale used in this study was based on the validated CGI scale, which is widely used as a simple tool to assess the overall effect of treatments. The subject was asked to rate her satisfaction with the study treatment according to the following scale: Score 1 = very much satisfied; Score 2 = much satisfied; Score 3 = minimally satisfied; Score 4 = neither satisfied nor dissatisfied; Score 5 = minimally dissatisfied; Score 6 = much dissatisfied; Score 7 = very much dissatisfied. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:
Weeks 12, 24, 36, 40, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	111[16]			
Units: Percentage of subjects				
number (not applicable)				
Week 12 (N=104): Score=1	27.9			
Week 12 (N=104): Score=2	46.2			
Week 12 (N=104): Score=3	15.4			
Week 12 (N=104): Score=4	5.8			
Week 12 (N=104): Score=5	1.9			
Week 12 (N=104): Score=6	1.9			
Week 12 (N=104): Score=7	1			
Week 24 (N=100): Score=1	39			
Week 24 (N=100): Score=2	45			
Week 24 (N=100): Score=3	8			
Week 24 (N=100): Score=4	6			
Week 24 (N=100): Score=5	2			
Week 24 (N=100): Score=6	0			
Week 24 (N=100): Score=7	0			
Week 36 (N=96): Score=1	44.8			
Week 36 (N=96): Score=2	40.6			
Week 36 (N=96): Score=3	10.4			
Week 36 (N=96): Score=4	3.1			
Week 36 (N=96): Score=5	0			
Week 36 (N=96): Score=6	1			
Week 36 (N=96): Score=7	0			
Week 40 (N=1): Score=1	0			
Week 40 (N=1): Score=2	100			
Week 40 (N=1): Score=3	0			
Week 40 (N=1): Score=4	0			
Week 40 (N=1): Score=5	0			
Week 40 (N=1): Score=6	0			
Week 40 (N=1): Score=7	0			
Week 52 (N=103): Score=1	47.6			
Week 52 (N=103): Score=2	36.9			
Week 52 (N=103): Score=3	8.7			
Week 52 (N=103): Score=4	4.9			
Week 52 (N=103): Score=5	0			
Week 52 (N=103): Score=6	1.9			
Week 52 (N=103): Score=7	0			

Notes:
[16] - FAS.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Safety-related Findings

End point title	Number of Safety-related Findings

End point description:

Safety-related findings such as blood pressure, heart rate, body weight, and laboratory examinations, were listed as adverse events.

End point type	Other pre-specified

End point timeframe:

Baseline up to 2 days after last dose of study drug (approximately 52 weeks)

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: Findings				

Notes:

[17] - Data for this endpoint were reported in adverse event (AE) section of the study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vaginal Bleeding Events by 90-day Reference Period

End point title	Vaginal Bleeding Events by 90-day Reference Period

End point description:

Bleeding episodes were described using the reference period (RP) method recommended by the World Health Organization over a RP of 90 days. Each subject recorded the vaginal bleeding patterns in their e-diaries. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	111[18]			
Units: Events				
arithmetic mean (standard deviation)				
Bleeding /spotting episodes in RP-1 (N=64)	3.1 (± 2.3)			
Bleeding /spotting episodes in RP-2 (N=51)	1.9 (± 2.1)			
Bleeding /spotting episodes in RP-3 (N=55)	1.5 (± 2.1)			

Bleeding /spotting episodes in RP-4 (N=44)	1.6 (± 2)			

Notes:

[18] - FAS.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Women With Pregnancy Test Result Over 52 Weeks

End point title	Number of Women With Pregnancy Test Result Over 52 Weeks

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, unscheduled visit, and 52

End point values	Dienogest (Visanne, BAY86-5258)			
Subject group type	Reporting group			
Number of subjects analysed	111[19]			
Units: Subjects				
Baseline (N=111): Positive	0			
Baseline (N=111): Negative	111			
Week 4 (N=110): Positive	0			
Week 4 (N=110): Negative	110			
Week 8 (N=107): Positive	0			
Week 8 (N=107): Negative	107			
Week 12 (N=104): Positive	0			
Week 12 (N=104): Negative	104			
Week 16 (N=103): Positive	0			
Week 16 (N=103): Negative	103			
Week 20 (N=100): Positive	0			
Week 20 (N=100): Negative	100			
Week 24 (N=102): Positive	0			
Week 24 (N=102): Negative	102			
Week 28 (N=100): Positive	0			
Week 28 (N=100): Negative	100			
Week 32 (N=97): Positive	0			
Week 32 (N=97): Negative	97			
Week 36 (N=99): Positive	0			
Week 36 (N=99): Negative	99			
Week 40 (N=97): Positive	0			
Week 40 (N=97): Negative	97			
Week 44 (N=97): Positive	0			
Week 44 (N=97): Negative	97			
Week 48 (N=95): Positive	0			

Week 48 (N=95): Negative	95			
Unscheduled visit (N=4): Positive	1			
Unscheduled visit (N=4): Negative	3			
Week 52 (N=108): Positive	0			
Week 52 (N=108): Negative	108			

Notes:

[19] - FAS.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 2 days after last dose of study drug (approximately 52 weeks)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Dienogest (BAY 86-5258)
Reporting group description:	
Subjects received Dienogest orally at a dosage of 2 mg once daily over a period of 52 weeks.	

Serious adverse events	Dienogest (BAY 86-5258)		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 111 (4.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Spinal column injury			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenomyosis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian adhesion			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dienogest (BAY 86-5258)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 111 (82.88%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Surgical and medical procedures			
Dental operation			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		

Orthodontic procedure subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Tooth repair subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Tonsillectomy subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Wisdom teeth removal subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Chills subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Discomfort subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Medical device pain subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Pyrexia subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6		
Fatigue subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2		
Malaise subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2		
Irritability			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Feeling cold			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Polycystic ovaries			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	4		
Ovarian cyst			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Metrorrhagia			
subjects affected / exposed	7 / 111 (6.31%)		
occurrences (all)	8		
Breast enlargement			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Menorrhagia			

subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	4		
Endometriosis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Endometrial hypertrophy			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Breast pain			
subjects affected / exposed	8 / 111 (7.21%)		
occurrences (all)	9		
Menstruation irregular			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Vulvovaginal pruritus			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Vaginal inflammation			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	7		
Vaginal discharge			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Uterine haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	3		
Oropharyngeal pain			

subjects affected / exposed	6 / 111 (5.41%)		
occurrences (all)	12		
Nasal inflammation			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	6 / 111 (5.41%)		
occurrences (all)	7		
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Tearfulness			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Panic disorder			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	7		
Mood altered			
subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Depressed mood			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	10		
Anxiety			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Libido decreased			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		

Investigations			
Weight decreased			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Blood sodium increased			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	10 / 111 (9.01%)		
occurrences (all)	10		
White blood cell count increased			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		

Muscle strain			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Excoriation			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Ligament injury			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Hand fracture			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Arthropod bite			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Post-traumatic pain			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Procedural pain			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Tooth fracture			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Cardiac disorders			
Tachycardia			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Nervous system disorders			
Poor quality sleep			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Somnolence			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	7		
Hypoaesthesia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	36 / 111 (32.43%)		
occurrences (all)	75		
Syncope			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Lymphadenitis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Myopia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Haematochezia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Glossitis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	8 / 111 (7.21%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	9 / 111 (8.11%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Abdominal pain upper			

subjects affected / exposed	5 / 111 (4.50%)		
occurrences (all)	6		
Abdominal pain lower			
subjects affected / exposed	7 / 111 (6.31%)		
occurrences (all)	10		
Flatulence			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Rectal haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Plicated tongue			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Odynophagia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	13 / 111 (11.71%)		
occurrences (all)	18		
Hyperchlorhydria			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Gastric disorder			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	16 / 111 (14.41%)		
occurrences (all)	22		
Toothache			
subjects affected / exposed	4 / 111 (3.60%)		
occurrences (all)	5		
Hepatobiliary disorders			

Cholecystitis subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	5 / 111 (4.50%) 6		
Seborrhoea subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Rash pruritic subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2		
Rash papular subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Rash subjects affected / exposed occurrences (all)	3 / 111 (2.70%) 3		
Alopecia subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2		
Eczema subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Cafe au lait spots subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Blister subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Psoriasis subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Torticollis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	6 / 111 (5.41%)		
occurrences (all)	12		
Tendonitis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	2		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Acute tonsillitis			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	6 / 111 (5.41%)		
occurrences (all)	6		
Candidiasis			

subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Chronic tonsillitis				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Cystitis				
subjects affected / exposed	8 / 111 (7.21%)			
occurrences (all)	8			
Ear infection				
subjects affected / exposed	3 / 111 (2.70%)			
occurrences (all)	4			
Fungal skin infection				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	16 / 111 (14.41%)			
occurrences (all)	17			
Nasopharyngitis				
subjects affected / exposed	35 / 111 (31.53%)			
occurrences (all)	61			
Otitis externa				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Otitis media				
subjects affected / exposed	2 / 111 (1.80%)			
occurrences (all)	2			
Gingivitis				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Periodontitis				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	7 / 111 (6.31%)			
occurrences (all)	8			
Gastroenteritis				

subjects affected / exposed	4 / 111 (3.60%)			
occurrences (all)	5			
Gastroenteritis viral				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Otitis media acute				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	5 / 111 (4.50%)			
occurrences (all)	8			
Pneumonia				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Pyelonephritis acute				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	3 / 111 (2.70%)			
occurrences (all)	3			
Scarlet fever				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	5 / 111 (4.50%)			
occurrences (all)	5			
Tonsillitis				
subjects affected / exposed	12 / 111 (10.81%)			
occurrences (all)	13			
Upper respiratory tract infection				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Vaginal infection				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences (all)	1			
Varicella				

subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Adenovirus infection			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Helminthic infection			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	3		
Vulvitis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences (all)	4		
Burn infection			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Tinea versicolour			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	5 / 111 (4.50%)		
occurrences (all)	8		
Oral herpes			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences (all)	1		

Lactose intolerance subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2010	In the initial study protocol, the study phase was termed as "Phase IV". The Austrian Health Authority (AGES) recommended a change of the study phase as "Phase II" in order to increase the focus on the latter aspects of the trial design.
19 May 2011	The following modifications were done in this protocol amendment: 1. Country specific change of inclusion criterion for Finland included study enrolment of 12 – 14 years old adolescents whose diagnosis of endometriosis had been confirmed by laparoscopy 2. Country specific change of requirements to perform gynecological examination in subjects below 15 years of age and written authorization of investigators
16 August 2012	Subjects with a decrease in BMD between baseline and end of treatment were invited for a follow-up scan of 6 months after the end of treatment in order to assess development of BMD after stopping study treatment. Data related to potential confounding parameters (height, weight, diet and medication) were also collected. A newly introduced Visit 17 was only to take place if there was a decrease in the lumbar spine BMD observed between Baseline (Visit 2) and End of Treatment (Visit 15). Introduced with this amendment, additional diagnostic procedures including a further BMD measurement of 12 months after end of treatment, and treatments were initiated as deemed necessary by the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported